4. MALFORMATIONS OF STRUCTURES DEVELOPED FROM THE NEURAL TUBE (B1-B7)

Anencephalus, hydrocephalus, spina bifida and similar defects occur all over the world and in many countries cause about half of the deaths attributable to congenital malformations. Most of these conditions are readily recognized, although in some instances where a spina bifida cystica is inconspicuous it may be missed, and, particularly in hospitals where the duration of stay of mothers is short, hydrocephalus recognizable only by post-natal enlargement of the head may not be detected.

There is probably some association of all these defects with maternal age and/or parity, although there are differences of view about these associations and their relative importance in the different types. Parity is so strongly correlated with maternal age in large series that standardization for the latter only is probably adequate for the purpose of removing both these influences before comparing frequencies.

However, of pregnancies where the child is found subsequently to have a neural tube defect, an undue proportion are complicated. Thus hydramnios occurs in 30%-50% of these pregnancies, toxaemia is possibly more frequent, and malpresentation is a common complication. Breech and transverse presentations often result from the gross malformation of the child and in the case of anencephalus, and in some cases of hydrocephalus, the head may not fix in the pelvis as expected late in the pregnancies of primigravidae.

Such pregnancy disturbances inevitably determine selective admission to hospital for confinement when the foetus has one of this group of malformations. The degree of such selection depends on the adequacy of the antenatal care and on the proportion of emergency admissions to a particular hospital, but it is not possible to measure with any confidence the relative selection intensities in different hospitals.

That this fact of selection is very strong may be illustrated by the situation in Belfast, where about 60% of mothers were confined in hospital and 40% at home. The frequency of anencephalus in hospital births was about three times as high as in home births (Stevenson & Warnock, 1959). As will be seen from Tables 4.1A, 4.1B and 4.2, there are large variations between centres in the frequencies standardized for maternal age of all these neural tube defects, but in view of the preceding remarks such differences, unless very large, are difficult to interpret.

ANENCEPHALUS ONLY (B1) AND ANENCEPHALUS AND SPINA BIFIDA (B2) IN SINGLE BIRTHS

Frequencies

There is a 40-fold difference in the frequency of all anencephalus (groups B1+B2) between the highest standardized frequency (in Belfast) and the lowest (Bogotá and Ljubljana) (Table 4.1A). In view of these large differences and of what is known from other sources about variations of frequencies both within and between countries (summarized by Penrose, 1957), there is little doubt that much of the variation reflects real population birth frequency differences and not only differing hospital admission policies. The other centre where the frequency of anencephalus with and without spina bifida is high is Alexandria (3.79 per 1000), and there were many cases also in Bombay (1.89 per 1000) and Mexico 1 (1.78 per 1000).

The frequencies standardized for maternal age for different neural tube malformations are directly additive and comparable in the data within a given country. The relative frequencies of anencephalus without spina bifida (B1) and with spina bifida (B2) may thus be compared with some confidence because both are equally obvious and therefore likely to be recognized at birth, although there may have been failures to mention a spina bifida in some instances. The two frequencies are, however, correlated in the different centres ($r = +0.611$; $P<0.005$).

On average, anencephalus alone is about seven times as frequent as anencephalus with spina bifida, but there is a large variation in the relative frequencies. The mean frequency over all centres of B1 and B2 is 1.05 per 1000 total births.

Sex proportions

Of all cases of B1 and B2, about two-thirds are in females. This female excess is well known, as is the variation in the proportion in different series

However, there is no evidence to support the suggestion sometimes made (e.g., Searle, 1959) that the higher the frequency of anencephalus, the smaller the female preponderance. The frequencies of B1 and B2 (standardized) and the size of the female/male ratio are not associated in the present data ($r = + 0.033$).

Frequencies of anencephalus in ethnic groups (single births)

It has been pointed out by several authors (e.g., Penrose 1957), that anencephalus is relatively uncommon in peoples of African origin. This view appears to be supported by the relatively low frequency in the Pretoria data, where the mothers were Bantu (0.50 per 1000 total births for all anencephalus, B1 and B2). The phenomenon is also suggested by published hospital reports from East and West Africa, not quoted by Penrose (1957) or others. For example, in 14 444 children born in the Makerere Hospital, Kampala, Uganda, between 1956 and 1958, there were only 8 cases (0.41 per 1000). It is noteworthy that in all these African hospitals over comparable periods hydrocephalus (not further specified) was from two to four times as frequent. The same situation holds in Pretoria in the present data. More information on this point is needed.

It will have been noted that the frequency of anencephalus in Indian mothers in Bombay is relatively high. There is an interesting situation in Fiji in that about half the population are indigenous Melanesians and the remainder of Indian origin. The frequency of anencephalus in the Colonial War Memorial Hospital, Fiji, over the period 1956-59 was 1 among 2791 in Fijians (0.33 per 1000) and 6 among 4494 in Indians (1.33 per 1000), which is suggestive of a real difference.[1]

Searle (1959), from the records of the Kandang Kerbau Hospital, Singapore, from 1953 to 1956, estimated that the frequency of anencephalus in offspring of Sikh mothers was very high—namely, 6.5 per 1000 births compared with 0.77 in all births. The number of Sikh mothers was estimated from a 1 in 18 sample of all births. His estimate of the frequency in other mothers of Indian origin was 0.69 per 1000 births.

In the present study the breakdown in ethnic groups was initially not taken further than Indian. Subsequently, however, Dr T. H. Lean had a 1 in 10 sample made of the births over the period of the study and it is estimated that there were about 400 Sikh mothers delivered. None of them gave birth to a child with anencephalus. The 2719 other Indian mothers gave birth to two anencephalics, a frequency of 0.73 per 1000 single births. (There was no case of anencephalus in twins in Singapore.) Since 1956 the number of births in the Kandang Kerbau Hospital has risen steadily and is now about 40 000 per year. The proportion of all births to Chinese mothers has remained constant or possibly fallen a little, and that of Indians has fallen considerably from 16.15% in 1953-56 to 7.8% over the period of the present study (which, for Singapore, was the year 1963). The proportion of Malay mothers rose from 2.79% in 1953-56 to 12.3% during the present study. From the present data there would thus not appear to be any evidence to support Searle's suggestion of a high incidence in Sikhs.

We are indebted to Professor C. Phillips for the following data from the Government Medical College, Amritsar in the Punjab, where the Sikhs originated. Over the years 1954-59 from 6308 deliveries of Sikh mothers, 25 anencephalic babies were born (3.96 per 1000). In the same period to 10 361 Hindu mothers 22 anencephalic babies were born (2.12 per 1000). The frequency to Hindu mothers is similar to that in Bombay and that in Sikhs is significantly higher ($P<0.05$).

In the study data from Belfast and Alexandria frequencies of anencephalus with and without spina bifida were remarkably high, as already noted. In both centres there is a strong association with hydramnios. (Some data on the associations of hydramnios, anencephalus and consanguinity will be published by Professor Toppozada.)

HYDROCEPHALUS ALONE (B3) AND HYDROCEPHALUS WITH SPINA BIFIDA (B4) IN SINGLE BIRTHS

The frequency of the conditions (B3 and B4) together over all centres is 0.87 per 1000 total births, or rather less than for anencephalus. There is, however, considerably less variation of frequencies between centres than for anencephalus (Table 4.1A). Again the highest frequencies are in Belfast (2.87 per 1000) and Alexandria (2.57 per 1000), with the Melbourne centres also having high frequencies (1.96 and 1.89 per 1000).

There is a positive correlation of frequencies of the two conditions B3 and B4 ($r = + 0.468$;

[1] Dr W. H. MacDonald, Medical Department, Suva—personal communication, 1960.

$P<0.01$). This suggests some common etiology. However, the varying sex proportions suggest some differences.

It will be noted that there is a small male excess in hydrocephalus without spina bifida (B3). There is, however, no significant difference between the sex proportions in B3 and B4. Nevertheless, a small male excess in hydrocephalus without spina bifida is present in most reported series of cases, and a sex proportion of less than 0.5 has almost invariably been found in cases of hydrocephalus and spina bifida. Part of the male excess in the former (B3) is probably due to cases determined by a sex-linked gene mutation which causes stenosis of the aqueduct of Sylvius (Edwards, 1961). It might be expected that these monomeric cases are underrepresented in the present series, in that not infrequently the hydrocephalus so caused only begins to be obvious some time after birth.

A majority of the cases of hydrocephalus with spina bifida are probably determined by the Arnold-Chiari malformation, where spina bifida is almost invariably present. In this condition there is a female excess in most reported series. The posterior " notching " of the foramen magnum into the occipital bone appears in many cases to be almost as severe as in cases of occipital meningocoele. That there are some etiological factors common to anencephalus, occipital meningocoele and Arnold-Chiari malformation is also suggested by the not infrequent occurrence of one of these conditions in one sib and another type in another sib. However, the correlations in frequency between the various neural tube defects shown in Table 4.3 and discussed below are difficult to reconcile with such a hypothesis.

It may be noted that only in a small number of cases was an autopsy diagnosis made of the type of hydrocephalus in the study (see the Basic Tabulations by Centres booklet).

OCCIPITAL MENINGOCOELE (B5)

This condition, which is relatively uncommon, as may be seen from Table 4.1B, is sometimes grouped by other writers with encephalocoele and sometimes with spina bifida. Both have some justification in that the meningocoele may project through the lower part of the occipital bone and often contains brain tissue, but other cases are associated with defective arches of the upper cervical vertebrae, so that the condition might be termed cervical spina bifida. However, as noted above, the condition also has similarities to the Arnold-Chiari malformation in that it appears, in some instances, to be determined by (or associated with) a similar but even larger defect of the occipital bone where it forms the posterior edge of the foramen magnum. In occipital meningocoele there is usually an excess of females, as in both Arnold-Chiari malformation and the spinal meningocoele. There is a female excess in the present data but the numbers are too small for any opinion to be expressed as to its interpretation.

SPINA BIFIDA (B6)

As may be seen from Table 4.1B spina bifida has a mean frequency of about 0.55 per 1000 total births. The term, as used, includes spina bifida cystica, whether the " cyst " is technically only a meningocoele (or a meningo-myelocoele) and also spinal rachischisis. It also includes these defects at all levels in the spine. Cases reported as " spina bifida occulta " only diagnosed by radiography have not been included.

The information given (as may be seen in the malformations lists) varied from " spina bifida (NFS) " to more precise descriptions of the types and locations of the lesions. It seems likely, if only from the great variation of location and degree, that there is some heterogeneity of etiology, although this is as yet undefined. It will be noted that there is a small female excess although it is not technically significant. The numbers of cases in many centres are small but the range of frequencies is less than for anencephalus. Again the frequency in Belfast is very high and that in Alexandria among the next highest.

OTHER NEURAL TUBE DEFECTS (B7)

Most cases in this group are encephalocoele and, as will be seen, the defects are uncommon relative to those of B1-B4 and B6, the mean frequency being less than 0.1 per 1000 total births.

RELATIVE FREQUENCIES OF THE DIFFERENT TYPES OF NEURAL TUBE DEFECTS (B1-B7) IN THE SAME COUNTRIES

Conclusions as to differences in frequencies between different countries can only be made with confidence if these differences are very large and the actual numbers of cases considerable. However, correlations of frequencies of the different types within countries can be made with more confidence,

particularly if maternal age standardized frequencies are used. This procedure removes a contribution to the correlation which might be present if maternal age distributions varied in different countries and some or all of the frequencies were in turn correlated with maternal age.

Table 4.3 sets out the correlations between the standardized frequencies of the different types and their significances. These correlations are made between standardized rates per 1000, so that the large numbers of cases in some centres such as Alexandria and Belfast each only contribute 1/24th to the correlation.

It is clear from the table that the frequencies of half of these neural tube defects are not independent of each other in the various countries. Although all these correlations in Table 4.2 are positive and some are statistically significant, no one correlation is significantly different in size from any other and it is therefore doubtful if much attention should be paid to their relative sizes.

Nevertheless, perhaps some comment should be made on the significant and non-significant correlated pairs of these malformations. If the five commonest and most easily definable malformations (B1, B2, B3, B4 and B6) are considered, it will be seen that the ten possible combinations are all significantly correlated at a 5% level. However, the four lowest of these ten correlations are those where hydrocephalus alone (B3) is one of the correlates.

The correlations between B1 and B7, B2 and B5, B3 and B5, and B3 and B7 are also significant at the levels shown on the table. The remaining seven correlations are all positive but not significant. However these findings are to be explained, they suggest that there are many common underlying factors predisposing to all the neural tube malformations. Such a view is supported by the well-known phenomenon of women who have had children with different neural tube defects.

THE IMPORTANCE OF NEURAL TUBE DEFECTS IN DETERMINING FATAL AND VERY SEVERE MALFORMATIONS

Table 4.2 sets out some data referring to the sum of all neural tube defects (B1-B7). It shows that the mean age of mothers of these cases is higher than that of mothers of non-malformed children. It shows also that, as might be expected from previous consideration of actual numbers and sex proportions of the individual groups of neural tube defects, the proportion of males is low and much lower than that in all other malformed children. In very few countries do these defects constitute less than 10% of all major malformations and they contribute high proportions of all those determining stillbirth or early death—over-all more than 50% of such deaths.

ASSOCIATED MALFORMATIONS

It will be remembered that the B1-B7 categories include infants with neural tube defects only and those with associated malformations, i.e., the latter are *not* classified in N. Although 75% of the infants were stillborn or died in hospital the proportion examined at autopsy was relatively small so that it must be presumed that many more than those recorded had other defects. Details of these associated malformations will be found in the Basic Tabulations by Centres booklet. Almost every other known malformation is found associated with neural tube defects, but it is noteworthy that any neural tube defect may be the sole malformation in a foetus otherwise perfectly developed as far as can be seen with the naked eye. If there are any other malformations they seldom are single but affect the heart, structures developed from the urogenital ridge and the skeleton, etc.

NEURAL TUBE DEFECTS IN TWINS

It is of interest that there is no example of anencephalus affecting both of a pair of twins in this series but it includes several twin pairs where one is affected. The phenomenon of one of a monozygous pair having anencephalus and the other being normal has been reported on many occasions (e.g., Litt & Strauss, 1935) whereas there is only one report where both twins of what was probably, but not certainly, a monozygous pair were affected (Josephson & Waller, 1933). There is one reported case where one of a pair of conjoined twins was affected and one was not (Mudaliar, 1930). While visiting the Kandang Kerbau Hospital, one of us was shown another example of this phenomenon by Dr T. H. Lean.

These observations suggest a minimal genotypic contribution to etiology and a rather localized uterine environmental causation. Such a hypothesis has to be reconciled with variations in frequency in different communities and variations by socio-economic levels in the same country, the latter so well shown in the vital statistical data from Scotland and elsewhere.

The occurrence of spina bifida and of hydrocephalus in twins is, however, by no means uncommon (Barr & Stevenson, 1961) and there are three examples in the present series (two in MM pairs and one in FF pairs) where one twin had hydrocephalus and spina bifida (B4) and the other spina bifida (B6). These observations are in accord with the high correlations of frequency of B4 and B6 and, together with the evidence of lesser socio-economic variations in frequency of spina bifida and hydrocephalus than in anencephalus, suggest a relatively more important genotypic contribution to these conditions than to anencephalus.

For convenience a summary of the twin pairs where one or both had a neural tube defect is set out in Table 4.4.

SUMMING-UP

The picture which emerges from these and other data concerning neural tube defects is a complex one. In all countries neural tube defects determine more stillbirths and early deaths than any other type of malformation, and there is much to suggest from the frequency correlations and occurrence of more than one type of these malformations in sibships that there are underlying causes common to most or all of these defects. The great majority of these defects have their origin in the early weeks of pregnancy and the very large socio-economic class and geographic variation within countries suggests strongly a major environmental contribution. This is also supported by the low frequency in monozygotic twins of concordance for the malformation, and in particular for anencephalus.

There is as yet no conclusive evidence for variation in frequency in different ethnic groups, and if such differences are detected even in peoples living in close proximity, their interpretation may be difficult in that there are almost invariably marked socio-economic differences between such groups living in the same countries.

The twin evidence points to the local intra-uterine environment being important and subtle differences in maternal nutrition or maternal/foetal relationships may be all-important. The relevant genetical situation could well be the nature of the maternal rather than the foetal genotype.

In the relatively few series of cases of neural tube defects previously studied where information on parental consanguinity has been available, no association has been demonstrated. In the present study some evidence of such an association is forthcoming. It is reviewed in section 19.

Whatever the nature of the genetical contribution to etiology, it can seldom, if ever, be determined at a single gene locus. Polman (1951), on the evidence of selected families, suggested that some cases of anencephalus might be due to a single recessive gene; but the condition is common, many women are encountered who have had two such infants, and cases have been reported and others referred to this unit where there have been three to five cases in a sibship. However, such evidence alone is not convincing, even if occasionally the parents are related. In man harmful recessive genes are fully manifest in homozygotes and multiple cases in sibships do not occur nearly frequently enough to meet the requirements of a single recessive hypothesis. Any genetical contribution is almost certainly multifactorial and not specifiable in the light of present genetical knowledge.

The data in Table 4.2 show how important these neural tube defects are all over the world whether assessed in terms of frequencies or mortality caused relative to all other malformations.

TABLE 4.1A

NEURAL TUBE DEFECTS (B1-B4) IN SINGLE BIRTHS: SEXES, MEAN MATERNAL AGES AND FREQUENCIES STANDARDIZED FOR MATERNAL AGE

CENTRE		Anencephalus only (B 1)						Anencephalus and Spina bifida (B 2)						Hydrocephalus only (B 3)						Hydrocephalus and Spina bifida (B 4)					
		Number of cases			Mean mat. age (yrs)	Freq. Stand mat. age	M/ M+F	Number of cases			Mean mat. age (yrs)	Freq. Stand mat. age	M/ M+F	Number of cases			Mean mat. age (yrs)	Freq. Stand mat. age	M/ M+F	Number of cases			Mean mat. age (yrs)	Freq. Stand. mat. age	M/ M+F
		M	F	T				M	F	T				M	F	T				M	F	T			
I 1	MELBOURNE	2	2	4	31.2	0.57	0.50	2	2	4	25.0	0.45	0.50	6	6	12	25.8	1.64	0.50	1	1	2	25.0	0.32	0.50
I 2	MELBOURNE	0	1	1	32.5	0.29	0/0	0	1	1	37.5	0.30	0/1	1	2	3	25.8	0.76	0.33	2	2	4	31.2	1.13	0.50
II	SAO PAULO	4	4	8	29.4	0.60	0.50	1	0	1	22.5	0.06	1.00	8	5	13	31.7	0.98	0.62	1	1	2	32.5	0.15	0.50
III	SANTIAGO	2	4	6	24.2	0.26	0.33	0	1	1	37.5	0.03	0/1	4	4	8	30.6	0.32	0.50	1	0	1	32.5	0.04	1.00
IV 1	BOGOTA	0	2	2	30.0	0.11	0/2	0	0	0	-	-	0/0	6	10	16	29.7	0.92	0.38	0	1	1	17.5	0.03	0/1
IV 2	MEDELLIN	0	5	5	26.5	0.26	0/5	1	0	1	22.5	0.05	1.00	6	1	7	36.1	0.30	0.86	0	0	0	-	-	0/0
V	CZECHOSLOVAKIA	2	8	10	24.5	0.42	0.20	0	1	1	22.5	0.04	0/1	7	0	7	31.8	0.63	1.00	2	3	5	26.5	0.25	0.40
VI	ALEXANDRIA	11	19	30	26.7	3.18	0.37	1	5	6	29.2	0.61	0.17	11	9	20	29.0	1.99	0.55	4	2	6	28.3	0.58	0.67
VII	HONG KONG	7	6	13	31.0	1.24	0.54	0	0	0	-	-	0/0	2	2	4	33.8	0.29	0.50	1	0	1	27.5	0.10	1.00
VIII 1	BOMBAY	17	43	60	27.2	1.74	0.28	2	4	6	26.7	0.15	0.33	19	11	30	29.2	0.73	0.63	6	6	12	26.2	0.29	0.50
VIII 2	CALCUTTA	3	3	6	26.7	0.32	0.50	0	1	1	37.5	0.09	0/1	1	0	1	27.5	0.05	1.00	0	0	0	-	-	0/0
IX 1	KUALA LUMPUR	5	12	17	28.7	1.00	0.29	0	1	1	27.5	0.06	0/1	10	6	16	27.5	1.04	0.62	0	0	0	-	-	0/0
IX 2	SINGAPORE	17	8	26[a]	26.0	0.67	0.68	0	2	2	27.5	0.05	0/2	4	5	9	28.6	0.23	0.44	0	0	0	-	-	0/0
X 1	MEXICO CITY	8	12	20	25.5	1.43	0.40	3	6	9	29.7	0.35	0.33	7	5	12	27.9	0.48	0.58	3	2	5	31.5	0.19	0.60
X 2	MEXICO CITY	1	1	2	32.5	0.14	0.50	0	0	0	-	-	0/0	1	2	3	27.5	0.21	0.33	3	0	3	27.5	0.20	1.00
XI	BELFAST	32	87	119	29.6	4.09	0.27	1	10	11	29.6	0.39	0.09	16	19	35	28.6	1.23	0.46	21	26	47	29.3	1.64	0.45
XII	PANAMA CITY	1	6	7	26.8	0.50	0.14	1	1	2	25.0	0.13	0.50	10	4	15[a]	24.2	0.92	0.71	2	0	2	25.0	0.13	1.00
XIII	MANILA	8	7	15	26.2	0.52	0.53	0	0	0	-	-	0/0	4	4	8	25.0	0.27	0.50	0	1	1	27.5	0.03	0/1
XIV 1	CAPE TOWN	2	0	2	25.0	0.76	1.00	0	0	0	-	-	0/0	1	1	2	25.0	0.82	0.50	0	0	0	-	-	0/0
XIV 2	JOHANNESBURG	4	3	7	28.2	0.66	0.57	1	1	2	27.5	0.11	0.50	5	1	6	24.2	0.48	0.83	0	1	1	22.5	0.07	0/1
XIV 3	PRETORIA	1	3	4	27.5	0.40	0.25	1	0	1	37.5	0.10	1.00	6	4	11[a]	26.1	1.13	0.60	4	1	5	30.5	0.51	0.80
XV	MADRID	5	11	16	31.6	0.63	0.31	0	0	0	-	-	0/0	4	3	7	27.5	0.31	0.57	1	3	4	32.5	0.15	0.25
XVI 1	LJUBLJANA	0	0	0	-	-	-	1	0	1	22.5	0.10	1.00	4	1	5	24.5	0.63	0.80	1	4	5	24.5	0.51	0.20
XVI 2	ZAGREB	1	1	2	25.0	0.20	0.50	1	2	3	22.5	0.28	0.33	1	3	4	25.0	0.51	0.25	0	1	1	27.5	0.11	0/1
	TOTAL	133	248	382[a]	28.1	0.92	0.35	16	38	54	28.2	0.13	0.30	144	108	254[a]	28.3	0.61	0.57	53	55	108	28.6	0.26	0.49

[a] Includes 1 of indeterminate sex.

TABLE 4.1B

NEURAL TUBE DEFECTS (B5-B7) IN SINGLE BIRTHS: SEXES, MEAN MATERNAL AGES AND FREQUENCIES STANDARDIZED FOR MATERNAL AGE

CENTRE		Occipital meningocoele (B 5)						Spina bifida (B 6)						Other neural tube (B 7)					
		Number of cases			Mean mat. age (yrs)	Freq. stand. mat. age	M/ M + F	Number of cases			Mean mat. age (yrs)	Freq. stand. mat. age	M/ M + F	Number of cases			Mean mat. age (yrs)	Freq. stand. mat. age	M/ M + F
		M	F	T				M	F	T				M	F	T			
I 1	MELBOURNE	1	2	3	25.8	0.37	0.33	2	1	3	34.2	0.44	0.67	0	0	0	-	-	0/0
I 2	MELBOURNE	0	0	0	-	-	0/0	2	1	3	29.2	0.80	0.67	0	0	0	-	-	0/0
II	SAO PAULO	1	0	1	17.5	0.05	1.00	6	8	14	26.4	1.01	0.43	1	0	1	27.5	0.08	1.00
III	SANTIAGO	0	1	1	27.5	0.05	0/1	5	5	10	24.8	0.37	0.50	0	2	2	27.5	0.10	0/2
IV 1	BOGOTA	1	0	1	17.5	0.03	1.00	1	0	1	22.5	0.07	1.00	0	1	1	27.5	0.07	0/1
IV 2	MEDELLIN	0	0	0	-	-	0/0	2	2	4	35.8	0.18	0.50	0	0	0	-	-	0/0
V	CZECHOSLOVAKIA	0	1	1	22.5	0.04	0/1	8	4	12	26.7	0.61	0.67	0	2	2	25.0	0.09	0/2
VI	ALEXANDRIA	1	1	2	25.0	0.24	0.50	2	4	8[a]	30.6	0.83	0.33	1	3	4	29.2	0.45	0.25
VII	HONG KONG	0	0	0	-	-	0/0	1	2	3	29.2	0.26	0.33	1	0	1	32.5	0.07	1.00
VIII 1	BOMBAY	0	2	2	27.5	0.04	0/2	12	18	30	26.3	0.75	0.40	1	1	2	30.0	0.05	0.50
VIII 2	CALCUTTA	0	0	0	-	-	0/0	1	1	2	30.0	0.13	0.50	1	0	1	17.5	0.03	1.00
IX 1	KUALA LUMPUR	0	0	0	-	-	0/0	1	2	3	27.5	0.19	0.33	0	0	0	-	-	0/0
IX 2	SINGAPORE	0	0	0	-	-	0/0	2	3	5	30.5	0.12	0.40	0	1	1	37.5	0.02	0/1
X 1	MEXICO CITY	1	2	3	30.8	0.12	0.33	8	8	16	27.2	0.63	0.50	0	1	1	32.5	0.04	0/1
X 2	MEXICO CITY	0	1	1	17.5	0.09	0/1	3	1	4	27.5	0.28	0.75	1	1	2	30.0	0.14	0.5
XI	BELFAST	0	1	1	22.5	0.03	0/1	28	43	71	27.4	2.59	0.39	1	6	7	27.5	0.24	0.14
XII	PANAMA CITY	0	0	0	-	-	0/0	5	5	10	27.0	0.71	0.50	1	0	1	22.5	0.06	1.00
XIII	MANILA	0	0	0	-	-	0/0	1	0	1	27.5	0.03	1.00	4	1	5	27.5	0.17	0.80
XIV 1	CAPE TOWN	0	0	0	-	-	0/0	2	0	2	25.0	0.82	1.00	1	0	1	37.5	0.26	1.00
XIV 2	JOHANNESBURG	0	0	0	-	-	0/0	3	6	9	23.6	0.73	0.33	1	0	1	32.5	0.12	1.00
XIV 3	PRETORIA	0	0	0	-	-	0/0	5	1	6	25.8	0.60	0.83	0	0	0	-	-	0/0
XV	MADRID	0	0	0	-	-	0/0	3	5	8	29.4	0.35	0.38	0	0	0	-	-	0/0
XVI 1	LJUBLJANA	0	0	0	-	-	0/0	0	3	3	29.2	0.33	0/3	0	1	1	22.5	0.10	0/0
XVI 2	ZAGREB	0	0	0	-	-	0/0	0	3	3	27.5	0.35	0/3	0	0	0	-	-	0/0
	TOTAL	5	11	16	25.0	0.04	0.31	103	126	231[a]	27.4	0.55	0.45	14	20	34	28.3	0.08	0.41

[a] Includes 2 of indeterminate sex.

TABLE 4.2
ALL NEURAL TUBE DEFECTS (B1-B7) IN SINGLE BIRTHS

CENTRE	Number of cases			Mean maternal age (years)		Frequency standardized for maternal age per 1000 total births	Sex proportion M/M + F		Cases of B 1 - B 7 per cent. of:		Deaths in cases B 1 - B 7 per cent. of deaths in all malf.
	M	F	T	Cases B 1 - B 7	All not malf.		Cases B 1 - B 7	All other malf.	All malf.	All malf. less D, H & I	
I 1 MELBOURNE	14	14	28	27.3	26.3	3.79	0.50	0.58	18.9	27.2	42.0
I 2 MELBOURNE	5	7	12	30.0	26.3	3.28	0.42	0.45	17.6	23.1	36.0
II SAO PAULO	22	18	40	28.7	26.4	2.93	0.55	0.60	17.3	22.3	47.0
III SANTIAGO	12	17	29	27.4	27.6	1.17	0.41	0.51	12.9	17.7	36.9
IV 1 BOGOTA	8	14	22	26.9	25.9	1.23	0.36	0.48	7.0	15.1	21.4
IV 2 MEDELLIN	9	8	17	32.4	27.7	0.79	0.53	0.61	7.4	10.9	29.0
V CZECHOSLOVAKIA	19	19	38	26.7	25.5	2.08	0.50	0.59	10.9	15.9	25.0
VI ALEXANDRIA	31	43	76[a]	28.1	28.1	7.88	0.42	0.60	68.5	72.4	81.6
VII HONG KONG	12	10	22	31.2	29.9	1.96	0.55	0.46	19.3	24.7	32.7
VIII 1 BOMBAY	57	85	142	27.4	26.8	3.75	0.40	0.61	41.9	48.5	75.4
VIII 2 CALCUTTA	6	5	11	27.5	25.6	0.62	0.55	0.54	18.6	22.4	52.9
IX 1 KUALA LUMPUR	16	21	37	28.1	28.2	2.29	0.43	0.52	22.2	27.2	42.5
IX 2 SINGAPORE	23	19	43[a]	27.8	28.1	2.09	0.55	0.52	12.5	18.9	53.5
X 1 MEXICO CITY	30	36	66	29.2	27.6	3.24	0.45	0.60	18.4	24.4	62.0
X 2 MEXICO CITY	9	6	15	27.0	27.3	1.06	0.60	0.53	9.7	16.9	33.3
XI BELFAST	99	192	291	28.8	27.8	10.21	0.34	0.49	53.5	63.7	78.2
XII PANAMA CITY	20	16	37[a]	25.5	25.1	2.45	0.56	0.53	11.2	24.3	52.4
XIII MANILA	17	13	30	26.2	27.6	1.02	0.57	0.56	11.9	14.7	30.0
XIV 1 CAPE TOWN	6	1	7	26.8	27.2	2.66	0.86	0.52	26.9	33.3	50.0
XIV 2 JOHANNESBURG	14	12	26	25.6	25.6	2.17	0.54	0.56	10.3	17.5	24.2
XIV 3 PRETORIA	17	9	27[a]	27.5	26.7	2.74	0.67	0.55	21.7	24.3	59.3
XV MADRID	13	22	35	30.4	29.6	1.44	0.37	0.51	13.3	21.6	27.1
XVI 1 LJUBLJANA	6	9	15	25.2	27.5	1.67	0.40	0.51	8.8	16.1	40.0
XVI 2 ZAGREB	3	10	13	25.2	26.3	1.45	0.23	0.60	12.1	19.7	32.3
TOTAL	469	606	1079[a]	28.1	27.2	2.59	0.44	0.54	20.4	29.0	49.8

[a] The difference between the total and the sum of the numbers of males and females is due to infants of indeterminate sex.

TABLE 4.3

CORRELATIONS OF MATERNAL AGE STANDARDIZED FREQUENCIES OF SPECIFIED NEURAL TUBE DEFECTS (B1-B7) IN SINGLE BIRTHS

Groups correlated		Coefficient of correlation (*r*)	Significance (P)
B1 and B2	Anencephalus only and Anencephalus and spina bifida	+ 0.611	< 0.005
B1 and B3	Anencephalus only and Hydrocephalus only	+ 0.514	< 0.02
B1 and B4	Anencephalus only and Hydrocephalus and spina bifida	+ 0.607	< 0.005
B1 and B5	Anencephalus only and Occipital meningocoele	+ 0.269	> 0.1
B1 and B6	Anencephalus only and Spina bifida	+ 0.749	< 0.001
B1 and B7	Anencephalus only and Other neural tube	+ 0.614	< 0.005
B2 and B3	Anencephalus and spina bifida and Hydrocephalus only	+ 0.691	< 0.001
B2 and B4	Anencephalus and spina bifida and Hydrocephalus and spina bifida	+ 0.576	< 0.005
B2 and B5	Anencephalus and spina bifida and Occipital meningocoele	+ 0.677	< 0.001
B2 and B6	Anencephalus and spina bifida and Spina bifida	+ 0.475	< 0.02
B2 and B7	Anencephalus and spina bifida and Other neural tube	+ 0.351	> 0.1
B3 and B4	Hydrocephalus only and Hydrocephalus and spina bifida	+ 0.450	< 0.05
B3 and B5	Hydrocephalus only and Occipital meningocoele	+ 0.622	< 0.005
B3 and B6	Hydrocephalus only and Spina bifida	+ 0.459	< 0.05
B3 and B7	Hydrocephalus only and Other neural tube	+ 0.429	< 0.05
B4 and B5	Hydrocephalus and spina bifida and Occipital meningocoele	+ 0.120	> 0.1
B4 and B6	Hydrocephalus and spina bifida and Spina bifida	+ 0.793	< 0.001
B4 and B7	Hydrocephalus and spina bifida and Other neural tube	+ 0.276	> 0.1
B5 and B6	Occipital meningocoele and Spina bifida	+ 0.080	> 0.1
B5 and B7	Occipital meningocoele and Other neural tube	+ 0.262	> 0.1
B6 and B7	Spina bifida and Other neural tube	+ 0.420	< 0.05

TABLE 4.4
NEURAL TUBE DEFECTS (B1-B7) IN TWINS

	Defects		No. of pairs
	Twin 1	*Twin 2*	
MM Pairs	Hydrocephalus (NFS)	Sirenomelia	1
	Anencephalus	Normal	6
	Hydrocephalus & spina bifida	Normal	2
	Spina bifida	Normal	2
	Twin 1	*Twin 2*	
FF Pairs	Hydrocephalus & spina bifida	Spina bifida	1
	Anencephalus	Down's syndrome	1
	Anencephalus	Normal	2
	Hydrocephalus	Normal	2
	Spina bifida	Normal	1
	Male twin	*Female twin*	
MF Pairs	Hydrocephalus	Normal	1
	Spina bifida	Normal	1
	Normal	Anencephalus & spina bifida	2
	Normal	Spina bifida	2
		Total	24